Inflammatory Activity in Multiple Atherosclerotic Plaques of Patients Dying of Acute Myocardial Infarction

RICARDO A. SARMIENTO[MTSAC, 1], FEDERICO BLANCO [†, 1], COLOMA PARISI[2], SEBASTIÁN FANDIÑO[2], GERARDO GIGENA[1], RODRIGO BLANCO[1], JORGE SZARFER[1], ALEJANDRO GARCÍA ESCUDERO[1], MIGUEL A. RICCITELLI [MTSAC, 1], LUIS VIDAL[†, 1]

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Address for reprints:
Dr. Ricardo A. Sarmiento
Department of Cardiology.
Hospital General de Agudos
"Dr. Cosme Argerich"
Av. Almirante Brown 240
(C1155ADP) Buenos Aires, Argentina
e-mail: rsarmiento@intramed.net

SUMMARY

Background
Data from clinical and histopathologic studies suggest that inflammation plays a key role in instability of atherosclerotic plaque as patients with acute coronary syndromes present diffuse inflammatory infiltrates in the coronary arteries.

Objectives
To assess and locate the distribution of vulnerable plaques and inflammatory infiltrates in patients who died of acute myocardial infarction.

Material and Methods
We examined the coronary arteries from 58 patients who died of myocardial infarction using light microscopy. The following variables were evaluated in culprit and non-culprit coronary arteries: presence of thrombus, plaque rupture, intraplaque hemorrhage and inflammatory infiltrate.

Results
The presence of thrombus and intraplaque hemorrhage was significantly greater in culprit coronary arteries compared to non-culprit vessels (69% versus 38%; $p<0.008$, and 69% versus 50%; $p<0.03$, respectively). There were no significant differences in the presence of inflammatory infiltrates in atherosclerotic plaques from culprit and non-culprit coronary arteries (77% versus 71%; p=ns).

Conclusion
Inflammatory activity was demonstrated in acute myocardial infarction affecting not only the infarct-related artery but also other coronary vessels. Plaque accident was also present in more than one coronary artery.

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Key words > Myocardial Infarction - Inflammation - Thrombosis - Atherosclerosis

Abbreviations > **AMI** Acute myocardial infarction

BACKGROUND

Traditionally, acute myocardial infarction (AMI) is believed to be caused by rupture of an unstable coronary artery plaque that appears as a single lesion on angiography. (1) Yet, i t is currently accepted that endothelial dysfunction, inflammation and humoral mechanisms are related to the development of coronary atheromatosis. In acute coronary syndromes plaque instability develops in a multifocal pattern. (2) In consequence, several unstable and disrupted plaques coexist; any one of these lesions might progress to total occlusion of a vessel and emerge as the cause of an infarct. (3-6) In a histopathologic study in patients with acute coronary syndromes, Mauriello et al. found widespread inflammation in more than one coronary artery. (7) Given the hypothesis of the presence of multifocal unstable lesions in AMI, we conducted a histopathologic study of the entire coronary tree in patients dying of AMI.

MATERIAL AND METHODS

Population

Between January 1998 and December 2005, we performed a histopathologic study of the hearts of 58 patients

[MTSAC] Full Member of the Argentine Society of Cardiology
†To apply as full member of the Argentine Society of Cardiology
[1] Department of Cardiology. *Hospital General de Agudos "Dr. Cosme Argerich"*. Autonomous City of Buenos Aires
[2] Department of Anatomical Pathology. *Hospital General de Agudos "Dr. Cosme Argerich"*. Autonomous City of Buenos Aires

who died of AMI. Infarction was defined according to the classic criteria (prolonged ischemic chest pain, increased creatine kinase levels by more than double the normal concentration, and development of new Q waves in at least two contiguous electrocardiographic leads - two out of three criteria-). (8) The time from symptom onset to death was ≤ 5 days for all cases and the autopsies were performed within 6 hours after death. Patients with neoplasms, autoimmune diseases and those with a history of an infectious condition 90 days before dying were excluded from the study.

Histopathologic study methods

Coronary arteries were carefully dissected and decalcified if necessary. Then they were embedded in paraffin. The vessels were cut transversely at 2-mm intervals along the coronary tree and arterial sections were stained with hematoxylin and eosin for further evaluation with light microscopy (Figure 1 A, B y C). A microtome was used to obtain arterial sections. Culprit and non-culprit coronary arteries were studied in all patients.

Infarct-related artery was determined according to the electrocardiographic findings and the histopathologic infarct area.

The following histologic variables were evaluated: 1) presence of thrombus, 2) plaque rupture, 3) intraplaque hemorrhage, and 4) inflammatory infiltrate (Figure 2 A-J).

These variables were defined as follows: (9)

1. Thrombus: a mass consisting of formed elements and fibrin that forms within a blood vessel, and is adhered to the injured endothelium. The thrombus may be mural (subocclusive) or occlusive.
2. Plaque rupture: defined by an area of fibrous cap disruption of an atheromatous plaque whereby the overlying thrombus is in continuity with the underlying necrotic core.
3. Intraplaque hemorrhage: entry of blood into the necrotic core with fibrin deposition.
4. Inflammatory cell infiltrate: presence of lymphocytes and monocytes in the subendothelium. According to the number of lymphocytes per high-power field (total magnification 40× - 400 with light microscope), instability was considered mild (5 to 10 lymphocytes), moderate (10 to 20) or severe (>20).

Statistical Analysis

Data were incorporated into an Excel® database and were analyzed by Statistix 7 software. Qualitative variables were expressed as numbers and percentages, and analyzed using chi square test or Fisher's exact test. Quantitative variables had non gaussian distribution and, therefore, were analyzed using Wilcoxon test and Kruskall-Wallis test. A p value < 0.05 was considered statistically significant.

RESULTS

The demographic characteristics of the population are described in Table 1.

Thrombi were present in 40 out of 58 culprit arteries (69%) and in 22 (38%) of non-culprit arteries: p < 0.008. Intraplaque hemorrhage was found in 40 (69%) culprit coronary arteries and in 29 (50%) of non-culprit vessels; p < 0.03. There were no significant differences in the presence of inflammatory infiltrates in atherosclerotic plaques from culprit (n = 45; 77%) and non-culprit coronary arteries (n = 41; 71%); (p=ns) (Table 2).

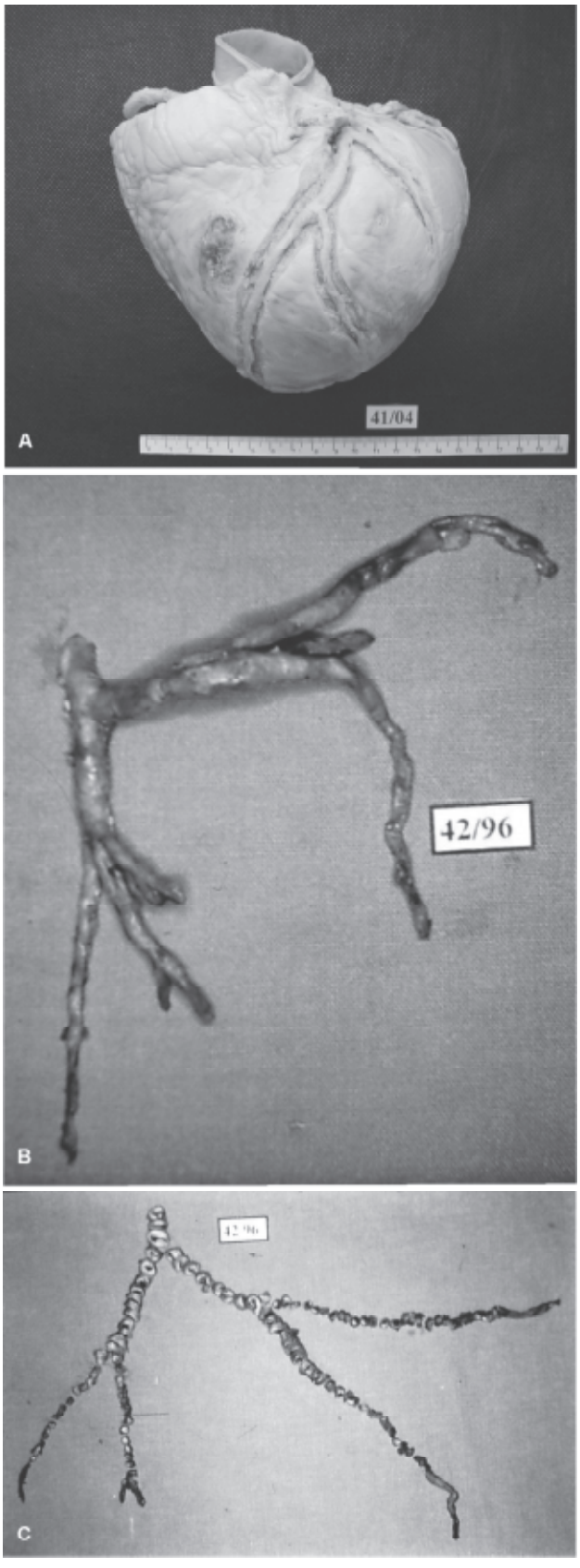

Fig. 1. A. Gross examination of the heart. **B.** Dissection of the coronary arteries. **C.** Transverse cut of the coronary arteries at 2-mm intervals along the coronary tree.

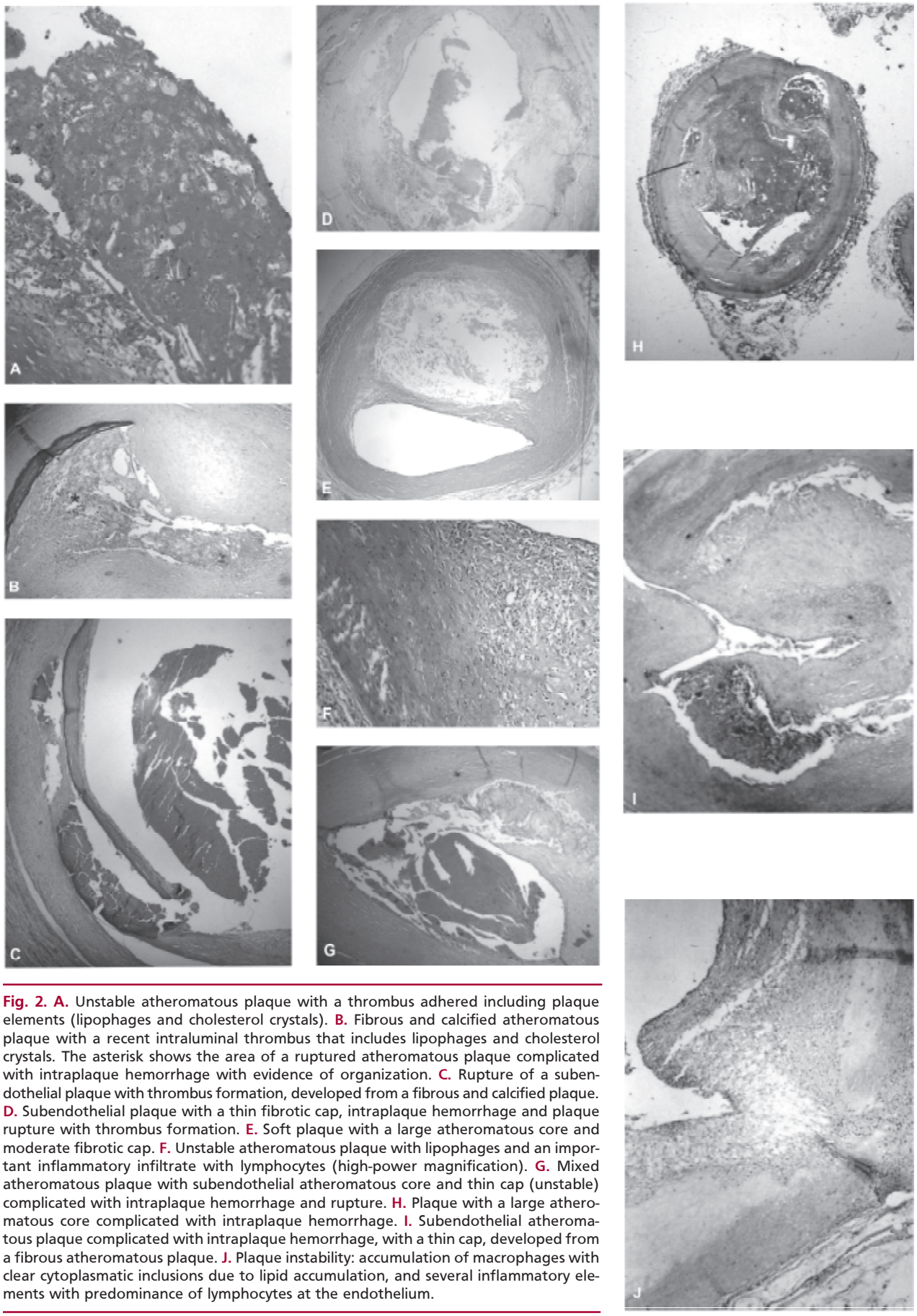

Fig. 2. A. Unstable atheromatous plaque with a thrombus adhered including plaque elements (lipophages and cholesterol crystals). **B.** Fibrous and calcified atheromatous plaque with a recent intraluminal thrombus that includes lipophages and cholesterol crystals. The asterisk shows the area of a ruptured atheromatous plaque complicated with intraplaque hemorrhage with evidence of organization. **C.** Rupture of a subendothelial plaque with thrombus formation, developed from a fibrous and calcified plaque. **D.** Subendothelial plaque with a thin fibrotic cap, intraplaque hemorrhage and plaque rupture with thrombus formation. **E.** Soft plaque with a large atheromatous core and moderate fibrotic cap. **F.** Unstable atheromatous plaque with lipophages and an important inflammatory infiltrate with lymphocytes (high-power magnification). **G.** Mixed atheromatous plaque with subendothelial atheromatous core and thin cap (unstable) complicated with intraplaque hemorrhage and rupture. **H.** Plaque with a large atheromatous core complicated with intraplaque hemorrhage. **I.** Subendothelial atheromatous plaque complicated with intraplaque hemorrhage, with a thin cap, developed from a fibrous atheromatous plaque. **J.** Plaque instability: accumulation of macrophages with clear cytoplasmatic inclusions due to lipid accumulation, and several inflammatory elements with predominance of lymphocytes at the endothelium.

Tabla 1. Demographic characteristics

Age (years), median (Q1, Q3)	63.5 (56.70)
Male gender, n (%)	46 (79.3%)
Current smoking, n (%)	39 (67.2%)
Dyslipemia, n (%)	29 (50%)
Diabetes, n (%)	7 (12%)
Hypertension, n (%)	31 (53.4%)

Tabla 2. Findings in culprit and non-culprit arteries

	Arteria responsable n (%)	Arterias no responsables n (%)	p
Presence of thrombus	40 (69)	22 (38)	0.008
Intraplaque hemorrhage	40 (69)	29 (50)	0.03
Inflammatory infiltrate	45 (77)	41 (71)	ns

DISCUSSION

The results of the present study show that thrombosis and hemorrhage occur not only in culprit atheromatous plaques but also in non-culprit lesions; however, these findings are significantly more frequent in the infarct-related coronary artery ($p < 0.008$; $p < 0.03$, respectively). Inflammatory activity was demonstrated in acute myocardial infarction affecting not only the infarct-related artery but also other coronary vessels. The results of our research are consistent with several studies that demonstrated the presence of multiple unstable plaques and thrombi in the coronary arteries of patients dying during the course of an AMI, and as a consequence of it; however, this finding has not been thoroughly analyzed until recently. (10-12)

Davies et al. (10) performed a histopathologic study of the coronary arteries of 74 patients who had died of AMI. They identified 115 plaque accidents corresponding to a mean of 1.55 plaque accidents per patient. The study by Falk (11) had similar results, with 103 different plaque ruptures in 44 cases. Frink (12) described the presence of multiple plaque accidents and thrombosis in a detailed study of necropsies performed on 83 patients dying of AMI. He found multiple ulcerated plaques in 71% of patients and 4 vulnerable lesions or greater in 20% of cases.

Baring these observations in mind, recent histopathologic studies focused on the hypothesis of the instability of multiple plaques. Mauriello et al. (7) compared the anatomy of the coronary arteries of patients dying of AMI ($n = 16$) with patients with stable angina ($n = 5$) and controls ($n = 9$, patients without coronary artery disease). In the group AMI, they found 6.8 ± 0.5 vulnerable segments in each patient, compared to 0.8 ± 0.3 and 1.4 ± 0.3 in patients with stable angina and controls, respectively. A significantly higher number of inflammatory cells was observed in the coronary trees of patients with AMI compared with the stable and control groups, independent of the type of plaque observed (121.6 ± 12.4 cells $\times$ mm^2 vs. 37.3 ± 11.9 cells $\times$ mm^2 v., 26.6 ± 6.8 cells $\times$ mm^2, respectively). (7) Interestingly, in patients with AMI there was inflammatory infiltrate in vulnerable plaques and in stable plaques. These results express a three- to four-fold higher inflammation activity in the culprit lesion and in stable plaques of patients dying of AMI, compared to patients with stable angina and controls. Therefore, this histopathologic study found that both coronary plaques of patients dying of AMI are diffusely infiltrated by inflammatory cells; these findings were not observed in the rest of the population analyzed. (7) These conclusions are coincidental with our findings.

Another histopathologic study was conducted by Sapgnoli et al., who analyzed the coronary arteries of 62 patients dying of AMI and found inflammatory cell infiltrates in the site of rupture of the infarct-related atherosclerotic plaque. (13) This finding was irrespective of the morphology of the plaque, suggesting that inflammation plays a relevant role. (13)

Following the same research line, the same work team conducted a study aimed at assessing the hypothesis that inflammation has a multifocal nature. Therefore, they studied the epicardial coronary arteries of 16 subjects dying of AMI in order to identify the cell components, and compared them with control subjects. Diffuse inflammatory infiltrate with activated T-lymphocytes were found in the infarct-related artery in all cases and in 69% of non-culprit arteries, (14) in contrast with lack of inflammation in control subjects. The total number of activated T-cells in the remote unaffected regions was significantly higher in cases with persistent infarct-related artery occlusion when compared with cases with non-occluded infarct-related arteries. These observations demonstrate the high prevalence of inflammatory cells within myocardial ischemia and confirm the evidence accumulated during the last years regarding the inflammatory nature of atherosclerosis. In turn, they also show us that the pattern of inflammation of AMI is characterized by a significant increase in the number of T-lymphocytes. (14)

In addition, a transient and significant increase in T-lymphocytes has been detected in patients with unstable angina, and inflammation of intramural coronary microvessels has also been demonstrated. (15-17) These data, together with the bibliography from other authors, suggest that activation of T-lymphocytes takes place in the scenario of AMI , and the release of gamma-interferon and other cytokines produce diffuse activation of several cell groups, including smooth-muscle cells, monocytes and macrophages in the branches of the epicardial coronary arteries.

(15, 18-20)This inflammatory substrate may lead to destabilization of coronary plaques in the entire coronary tree which may trigger a thrombotic process, depending on the different characteristics of the local anatomy and blood flow. (21, 22)

Other diagnostic methods have been used to assess the presence of multiple complex coronary plaques. Goldstein et al. (3) analyzed coronary angiograms of patients in the acute phase of myocardial infarction and demonstrated the presence of multiple complex plaques in a group of patients, (40%) defined by at least two out of four criteria: thrombus, ulceration, plaque irregularity, and impaired flow. These patients had worse short-term and intermediate-term outcomes, including repeated revascularization of the related artery and of other non-culprit complex lesions. Patients with multiple complex plaques had greater depression of left ventricular function than those with single complex plaques. The presence of multiple complex plaques was independently predictive of clinical events during the year after the AMI. (3)

Bemis et al. had already seen in 1973 significant progression of coronary artery disease in 52% of subjects studied by selective coronary angiography at 23.8 months. (23) A few years later, Kramer et al. demonstrated the same phenomenon in 65% of patients who had suffered an AMI. (24)

Guazzi et al. reported the evidence of multifocal activity in subjects with coronary artery disease. (25) These authors performed coronary angiography in 44 patients with AMI and in controls to compare the outcomes of the atherosclerotic lesions. They observed that the number of progressing lesions at the level of the offending plaque was greater in patients who had suffered an AMI. As a whole, 49% of non-culprit lesions appeared to be unstable in the postinfarction period; 38% showed progression as well as a tendency towards complex morphology and 11% showed regression and loss of complexity. (25) Although these findings are interesting, several crucial points should be considered mainly because coronary angiography in this particular setting is not the ideal method to assess such a dynamic process as atherosclerotic disease. Another limitation of the angiographic method is the inability to detect lesions that present positive coronary artery remodeling. Therefore, up to now coronary angiography has failed to achieve the exact incidence of active atheromatous lesions.

Intravascular ultrasound has been used to assess the presence of multiple complex lesions in the entire coronary tree. The association of this method with histopathologic study confirmed the relationship between eccentric remodeling, unstable plaques and acute coronary syndromes, whereas concentric remodeling was more common in patients with fibrous plaques and stable angina. (26) Rioufol et al. performed intracoronary ultrasound in the three main epicardial coronary arteries of 24 patients admitted with an acute coronary syndrome with troponin T elevation. (27) They detected 50 plaque accidents (mean, 2.08 per patient). Nineteen patients (79%) had at least 1 plaque rupture somewhere other than on the culprit lesion, 70.8% had at least 1 rupture diagnosed in an artery other than the culprit artery, and 12.5% had at least 1 rupture in all 3 arteries This information is similar to the findings published by Tanaka, who used intravascular ultrasound to investigate the presence of plaque accidents in non-culprit coronary arteries from patients with acute coronary syndrome. (28) Intravascular ultrasound revealed that 24% of patients had additional plaque ruptures at remote sites. Patients with multiple plaque accidents had multiple risk factors and worse outcomes. (28) Initial observations with intravascular ultrasound showed that the prevalence of multiple plaque rupture was 79%; however, subsequent studies demonstrated that this method can recognize 25-30% of multiple complex plaques in the scenario of acute coronary syndromes. (29, 30)

In the last years, several studies have found a strong correlation between the inflammatory process and increased local temperature measured with the use of thermography catheters. This method is used for functional assessment of atherosclerotic plaques to determine the underlying inflammatory process. (31-33) Atheromatous plaques of patients with acute coronary syndromes have higher temperature than plaques from patients with stable angina. Other studies found two or more “hot plaques” in patients with acute coronary syndromes. (32, 33) These findings were confirmed by a recent publication, which also puts into evidence that patients treated with statins had lower plaque temperature. These results support the hypothesis of a generalized inflammatory process in acute coronary syndromes. (34)

The information provided by our study demonstrates the presence of vulnerable plaques not only in the infarct-related artery but also in non-culprit coronary arteries. The diffuse inflammatory infiltrate suggests that inflammation plays a key role in the pathogenesis of acute coronary syndrome.

One of the limitations of our study is the absence of a control group of patients who had died due to other conditions. In addition, we did not use immunohistochemical techniques to differentiate T-lymphocytes. However, hematoxylin and eosin stain allowed to detect the presence of lymphocytes in several plaques studied.

CONCLUSION

Inflammatory activity was demonstrated in acute myocardial infarction affecting not only the infarct-related artery but also other coronary vessels. Plaque accident was also detected in more than one coronary artery.

RESUMEN

Actividad inflamatoria en múltiples placas ateroscleróticas en pacientes fallecidos por infarto agudo de miocardio

Introducción
Estudios clínicos y anatomopatológicos sugieren que los procesos inflamatorios tienen un papel importante en la inestabilidad de la placa aterosclerótica, dado que en pacientes con síndromes coronarios agudos se observan infiltrados inflamatorios difusos en las arterias coronarias.

Objetivos
Evaluar y localizar la distribución de placas vulnerables e infiltrados inflamatorios en pacientes fallecidos por infarto agudo de miocardio.

Material y métodos
Mediante microscopia óptica se estudiaron las arterias coronarias de 58 pacientes fallecidos por infarto de miocardio. En las arterias coronarias relacionadas con el infarto y en las no relacionadas se registraron las siguientes variables: presencia de trombo, rotura de placa, hemorragia intraplaca y presencia de infiltrado inflamatorio.

Resultados
Al analizar las diferencias existentes entre las arterias responsables del infarto y en las no responsables se encontraron diferencias significativas con respecto a la presencia de trombo (69% *versus* 38%; $p < 0,008$) y de hemorragia intraplaca (69% *versus* 50%; $p < 0,03$). No se encontró una diferencia significativa entre la arteria responsable y la no responsable al evaluar la presencia de infiltrado inflamatorio en las placas ateroscleróticas (77% *versus* 71%; p = ns).

Conclusión
En el infarto agudo de miocardio se comprobó la presencia de actividad inflamatoria que afectaba a más de un vaso, con compromiso de otras arterias además de la responsable del infarto. Se detectó también accidente agudo de placa en más de una arteria coronaria.

Palabras clave > Infarto del miocardio - Inflamación - Trombosis - Aterosclerosis

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